REMARKS

Claim 42 has been amended simply for clarity; since there is only one antineoplastic agent required by the claim, "first" has been deleted and the typographical error inserting a dash between "comprising" and "liposomes" has been removed.

Claim 42 has also been clarified to note explicitly that the drug resistance-modulating agent does not have antineoplastic activity itself. This clarification is supported in the specification in paragraph 28 which defines a "drug resistance modulator" as an agent that sensitizes a drug-resistant target to the effect of one or more therapeutic agents. As noted at the top of page 10, the modulator may itself exhibit therapeutic activity or, in the alternative claimed here, it may be inactive and thus act only to potentiate the effect of the therapeutic agent. That is the type of drug resistance-modulating agent that applicants intend to claim. Synergism in this context, then, would mean that the effect of the antineoplastic agent is potentiated by the presence of the drug resistance-modulating agent.

New claims 47 and 48 are narrower forms of the pending claims. These claims are supported in the specification in paragraph 35 (ABC transporter inhibitors), paragraph 36 (verapamil and staurosporine), paragraph 39 (lung resistance protein transporter), and paragraph 40 (glutathione-S-transferase, ethacrynic acid, buthionine sulfoximine).

No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention is directed to a *method* to prepare a pharmaceutical composition. The active components in the composition are an antineoplastic agent and a drug resistance-modulating agent. Claim 42 has been clarified and limited to the circumstance wherein the drug resistance-modulating

agent does not itself have antineoplastic activity. Its activity is confined to potentiating the effect of the antineoplastic agent that is also present. These are stably associated with liposomes so as to result in a coordinated delivery of a synergistic ratio which is first determined *in vitro*. The appropriate query is, therefore, not whether the prior art suggests a composition comprising liposomes containing these types of compounds, but whether the *method* itself is suggested by the art. Respectfully, it is not.

The Rejections

Claims 42-46 were rejected as assertedly obvious over Engblom (*Brit. J. Cancer* (1999)), or Kano (*Leukemia Res.* (1993)), or Guichard (*Biochem. Pharmacol.* (1998)) in combination with applicants' statements in further combination with Vaage (*Int. J. Cancer* (1993)), Saxon (*J. Liposome Res.* (1999)) or Bally (U.S. 5,736,155) individually or in combination. Respectfully, not a single one of these documents even mentions an essential element of the presently claimed method — *i.e.*, a drug resistance-modulating agent. Accordingly, there can be no suggestion of the method as claimed and this basis for rejection should be withdrawn.

Claims 42-46 were rejected as assertedly obvious over Engblom or Kano or Guichard in combination with Vaage, Saxon or Bally in further view of Giles (US2003/0083316). Giles is cited as describing using the CalcuSyn software based on Chou and Talalay to determine non-antagonistic ratios *in vitro*. Once again, however, there is no mention in any document of an essential element of the claims which is a drug resistance-modulator. Accordingly, this rejection, too, may be withdrawn.

The two foregoing rejections are therefore obviated at least on the ground that none of the cited documents even mentions a drug resistance-modulating agent — an essential element of the claimed subject matter.

Claims 42-46 were rejected as assertedly obvious over Matsuo (*J. Controlled Release* (2001) 77:77-86) or Krishna (*Int. J. Cancer* (2000) 85:131-141), or Singh (*Eur. J. Pharma. & Biopharma.* (2001) 52:13-20), or Sadasivan (*Cancer Let.* (1991) 57:165-171). This is made either over the documents themselves or in combination with statements of record.

Apparently the statements of record are that various algorithm methods, including Chou-Talalay median effect method are available to determine the synergistic activity of anticancer drugs. Applicants note that the invention requires applying this method to the combination of antineoplastic agent and a drug resistance-modulator, and further requires that the synergistic ratio obtained be put into liposomes to result in *coordinated* delivery of the synergistic ratio thus determined. Thus both the antineoplastic agent and the drug resistance modulator must be put into liposomes. Respectfully, none of the cited documents supply these missing elements.

As noted above, the suitable question is not whether the prior art suggests a composition comprising liposomes containing the compounds set forth in the claim, but whether the method of preparing such a composition is suggested by the art.

Matsuo employs vincristine encapsulated in liposomes that are coupled to the tumor targeting agent MRK-16, which also acts as a drug resistance modulator by binding to P-gp. Since the MRK-16 is part of the liposome structure itself, it is difficult to see how the method of the invention could be performed. The behavior of free MRK-16 and liposome-modified MRK-16 would not necessarily be the same, begging the question of what should be used in an *in vitro* assay

to determine synergism over a concentration range. This is especially true in view of the targeting function of MRK-16. As the Examiner is kind enough to note, Matsuo lacks any suggestion whatsoever of first determining the amounts of vincristine and MRK-16 that are synergistic *in vitro*. Applicants submit that the secondary documents do not overcome this deficiency. Applicants further note that when the drug resistance modulator verapamil is tested in Matsuo, it is supplied in free form, not in a liposomal formulation.

Krishna describes the ability of valspodar to enhance the efficacy of liposomal doxorubicin. There is no suggestion of determining a synergistic effect over a concentration range, nor is there any suggestion that coordinated pharmacokinetics be assured. Indeed, valspodar was supplied as a free drug and not included in liposomes.

Singh describes a combination of monensin and anti-My9 in liposomes, but makes no mention of determining a synergistic effect with an antineoplastic agent over a concentration range. The antineoplastic agent itself, an immunotoxin, is supplied in free form, not in liposomes, so there are no coordinated pharmacokinetics.

Similarly, Sadasivan simply teaches that verapamil can enhance the uptake of doxorubicin but the verapamil is not encapsulated or associated with liposomes and there is no suggestion of determining a synergistic ratio over a concentration range, an essential aspect of the presently claimed method.

Thus, none of the documents cited above suggests determining favorable synergistic ratios *in vitro* using an algorithm or by any other method. Applicants' statement of record as to the existence of such methods does not amount to a suggestion in the art that they be used in the contexts set forth above. Further, all of the documents essentially teach away from the invention by

administering the drug resistance modulators in free form rather than in a liposomal formulation, with the exception of the MRK-16 of Matsuo which is used simply as a targeting agent.

The Office asserts that assuming that the amounts in these documents are not synergistic it would be obvious to prepare the liposomes with amounts of active agents that are synergistic. The Office asserts that *in vitro* determination of the synergistic amounts is well known in the art. What is not suggested anywhere in the art is determining over a concentration range the synergistic ratio of a drug resistance modulator and an antineoplastic agent, or placing this ratio into liposomes. No document produced by the Office makes this suggestion. Indeed, the only document (Matsuo) that even discloses administering *both* an antineoplastic agent and a drug resistance modulator in liposomal form, describes an embodiment that would defy successful performance of the invention method.

Accordingly, this basis for rejection may also be withdrawn.

Double-Patenting

Claims 42-46 were provisionally rejected as obviousness-type double-patenting over claims 14, 16-17, 22-23 and 26-27 of copending application 11/304,328. This basis for rejection is inapposite for the same reasons that the first two rejections in the present case are inapposite; the claims in that application concern synergy between two antineoplastic drugs, not synergy between an antineoplastic drug and drug resistance modulator without antineoplastic activity.

Accordingly, this basis for rejection may also be withdrawn.

Conclusion

None of the cited documents suggest the method of the invention which requires determining a synergistic ratio of a drug resistance-inhibitor and an antineoplastic agent *in vitro* and

then stably encapsulating this ratio in liposomes. Accordingly, applicants believe claims 42-48 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor matters remain that could be resolved over the phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532552001000.

Respectfully submitted,

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